

General

Guideline Title

Practice parameter update: management issues for women with epilepsy--focus on pregnancy (an evidence-based review): teratogenesis and perinatal outcomes. Report of the Quality Standards Subcommittee and Therapeutics and Technology Subcommittee of the American Academy of Neurology and American Epilepsy Society.

Bibliographic Source(s)

Harden CL, Meador KJ, Pennell PB, Hauser WA, Gronseth GS, French JA, Wiebe S, Thurman D, Koppel BS, Kaplan PW, Robinson JN, Hopp J, Ting TY, Gidal B, Hovinga CA, Wilner AN, Vazquez B, Holmes L, Krumholz A, Finnell R, Hirtz D, Le Guen C. Practice parameter update: management issues for women with epilepsy--focus on pregnancy (an evidence-based review): teratogenesis and perinatal outcomes. Report of the Quality Standards Subcommittee [trunc]. *Neurology*. 2009 Jul 14;73(2):133-41. [45 references] [PubMed](#)

Guideline Status

This is the current release of the guideline.

The American Academy of Neurology reaffirmed the currency of this guideline in 2016.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

Definitions of the levels of the recommendations (A, B, C, U) and classification of the evidence (Class I-IV) are provided at the end of the "Major Recommendations" field.

Do antiepileptic drugs (AEDs) taken during the first trimester of pregnancy increase the risk of major congenital malformations (MCMs) in the offspring of women with epilepsy (WWE) compared to the offspring of WWE not on AEDs?

Conclusions

- AEDs taken during the first trimester probably increase the risk of MCMs in the offspring of WWE (two adequately sensitive Class II studies) but it cannot be determined if the increased risk is imparted from all AEDs or from only one or some AEDs.
- Valproate (VPA) monotherapy during the first trimester possibly increases the risk of MCMs in the offspring of WWE (one Class II study).
- VPA used in polytherapy probably increases the risk of MCMs in the offspring of WWE (one Class I study).
- Carbamazepine (CBZ) probably does not substantially increase the risk of MCMs in the offspring of WWE (one Class I study).
- There is insufficient evidence to determine if lamotrigine (LTG) (one inadequately sensitive Class I study) or other specific AEDs (no Class III or better evidence) increase the risk of MCMs in the offspring of WWE.

Recommendations

- Although there is evidence that AEDs taken during the first trimester probably increase the risk of MCMS in the offspring of WWE, it cannot be determined if the increased risk is imparted from all AEDs or from only one or some AEDs. Therefore, no recommendation is made from this conclusion.
- If possible, avoidance of the use of VPA as part of polytherapy during the first trimester of pregnancy should be considered to decrease the risk of MCMS (Level B).
- If possible, avoidance of the use of VPA monotherapy during the first trimester of pregnancy may be considered to decrease the risk of MCMS (Level C).

Is exposure to a specific AED during the first trimester of pregnancy associated with an increased risk of MCMS compared to exposure to other AEDs?

Conclusions

- It is highly probable that taking VPA monotherapy during the first trimester of pregnancy contributes to the development of MCMS in the offspring of WWE compared to taking carbamazepine (CBZ) (two Class I studies).
- VPA as part of polytherapy in the first trimester of pregnancy probably contributes to the development of MCMS in the offspring of WWE compared to polytherapy that does not include VPA (one Class I study).
- Taking VPA during the first trimester of pregnancy possibly contributes to the development of MCMS in the offspring of WWE compared to taking phenytoin (PHT) (one Class II study).
- Taking VPA during the first trimester of pregnancy possibly contributes to the development of MCMS in the offspring of WWE compared to taking LTG (two Class III studies).

Recommendations

- To reduce the risk of MCMS, the use of VPA during the first trimester of pregnancy should be avoided, if possible, compared to the use of CBZ (Level A).
- To reduce the risk of MCMS, avoidance of the use of polytherapy with VPA during the first trimester of pregnancy, if possible, should be considered, compared to polytherapy without VPA (Level B).
- To reduce the risk of MCMS, avoidance of the use of VPA during the first trimester of pregnancy, if possible, may be considered, compared to the use of PHT or LTG (Level C).

Is the risk of MCMS greater for AED polytherapy compared to AED monotherapy when taken during the first trimester of pregnancy?

Conclusion

- Polytherapy probably contributes to the development of MCMS in the offspring of WWE as compared to monotherapy (one Class I study).

Recommendation

- To reduce the risk of MCMS, avoidance of the use of AED polytherapy during the first trimester of pregnancy, if possible, compared to monotherapy should be considered (Level B).

Is there a relationship between AED dose and the risk of MCMS in the offspring of WWE?

Conclusion

- There is probably a relationship between the dose of VPA and LTG and the risk of development of MCMS in the offspring of WWE (one Class I study).

Recommendation

- Limiting the dosage of VPA or LTG during the first trimester, if possible, should be considered to lessen the risk of MCMS (Level B).

Are there specific MCMS associated with specific AEDs?

Conclusions

- PHT exposure in utero possibly contributes to the risk of cleft palate (one Class II study).
- CBZ exposure in utero possibly contributes to the risk of posterior cleft palate (one Class II study).

- VPA exposure in utero probably contributes to neural tube defects and facial clefts (one Class I study) and possibly contributes to hypospadias (one Class II study).
- Phenobarbital (PB) exposure in utero possibly contributes to cardiac malformations (two Class III studies).

Recommendations

- Avoidance of the use of VPA, if possible, should be considered to reduce the risk of neural tube defects and facial clefts (Level B) and may be considered to reduce the risk of hypospadias (Level C).
- Avoidance of phenobarbital (PHT), CBZ, and PB, if possible, may be considered to reduce the risk of specific MCMs: cleft palate for PHT use, posterior cleft palate for CBZ use, and cardiac malformations for PB use (Level C).

Is cognitive outcome reduced in children of WWE who are not exposed to AEDs in utero?

Conclusion

- Cognition is probably not reduced in children of WWE who are not exposed to AEDs in utero (two Class II studies).

Recommendation

- Counseling of WWE who are contemplating pregnancy should reflect that there is probably no increased risk of reduced cognition in the offspring of WWE not taking AEDs (Level B).

Is cognition reduced in children of WWE exposed to AEDs in utero?

Conclusions

- There is insufficient evidence to determine if the children of WWE on AEDs in general are at increased risk for reduced cognition (conflicting Class II studies).
- CBZ probably does not increase poor cognitive outcomes compared to unexposed controls (two Class II studies).
- VPA is probably associated with poor cognitive outcomes compared to unexposed controls (two Class II studies).
- PHT is possibly associated with poor cognitive outcomes compared to unexposed controls (one Class II and two Class III studies).
- PB is possibly associated with poor cognitive outcomes in male offspring of WWE compared to unexposed controls (two Class III studies).

Recommendations

- CBZ exposure probably does not produce cognitive impairment in offspring of WWE (Level B).
- Avoiding VPA in WWE during pregnancy, if possible, should be considered to reduce the risk of poor cognitive outcomes (Level B).
- Avoiding PHT in WWE during pregnancy, if possible, may be considered to reduce the risk of poor cognitive outcomes (Level C).
- Avoiding PB in WWE during pregnancy, if possible, may be considered to reduce the risk of poor cognitive outcomes (Level C).

Does AED polytherapy exposure during pregnancy pose an increased risk for poor cognitive outcome compared to monotherapy?

Conclusion

- Cognitive outcomes are probably reduced in children exposed to AED polytherapy as compared to monotherapy in utero (three Class II studies).

Recommendation

- Monotherapy should be considered in place of polytherapy, if possible, for WWE who take AEDs during pregnancy to reduce the risk of poor cognitive outcomes (Level B).

Is exposure to a specific AED in utero associated with poor cognitive outcomes compared to other AEDs?

Conclusions

- Cognitive outcomes are probably reduced in children exposed to VPA during pregnancy compared to CBZ (two Class II studies).
- Cognitive outcomes are possibly reduced in children exposed to VPA during pregnancy compared to PHT (one Class II study).

Recommendations

- For WWE who are pregnant, avoidance of VPA, if possible, should be considered compared to CBZ to reduce the risk of poor cognitive

outcomes (Level B).

- For WWE who are pregnant, avoidance of VPA, if possible, may be considered compared to PHT to reduce the risk of poor cognitive outcomes (Level C).

Is there an increased risk of small for gestational age (SGA) outcomes in neonates born to WWE?

Conclusion

- Neonates of WWE taking AEDs probably have an increased risk of SGA of about twice the expected rate (two Class II studies).

Recommendation

- Pregnancy risk stratification should reflect that the offspring of WWE taking AEDs during pregnancy probably have an increased risk of SGA. Further, AED use in WWE during pregnancy should be considered in the differential diagnosis of SGA in their offspring (Level B).

Is there an increased risk of perinatal death in neonates born to WWE?

Conclusion

- There is probably no substantially increased risk of perinatal death in neonates born to WWE (two Class II studies).

Recommendation

- Pregnancy risk stratification should reflect that neonates born to WWE probably do not have a substantially increased risk of perinatal death (Level B).

Are Apgar scores lower in neonates born to WWE?

Conclusion

- Neonates of WWE taking AEDs possibly have an increased risk of 1-minute Apgar scores of <7 of about twice the expected rate (one Class II study).

Recommendation

- Pregnancy risk stratification should reflect that the offspring of WWE taking AEDs during pregnancy possibly have an increased risk of 1-minute Apgar scores of <7. Further, AED use in WWE during pregnancy may be considered in the differential diagnosis of a 1-minute Apgar score of <7 in their offspring (Level C).

Definitions:

Classification of Recommendations

The strength of practice recommendations is linked directly to the level of evidence:

Level A = Established as effective, ineffective, or harmful (or established as useful/predictive or not useful/predictive) for the given condition in the specified population. (Level A rating requires at least two consistent Class I studies.*)

Level B = Probably effective, ineffective, or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specified population. (Level B rating requires at least one Class I study or two consistent Class II studies.)

Level C = Possibly effective, ineffective, or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population. (Level C rating requires at least one Class II study or two consistent Class III studies.)

Level U = Data inadequate or conflicting; given current knowledge, treatment (test, predictor) is unproven.

*In exceptional cases, one convincing Class I study may suffice for an "A" recommendation if: 1) all criteria are met, 2) the magnitude of effect is large (relative rate improved outcome >5 and the lower limit of the confidence interval is >2).

Classification of Recommendations for Causality

Level A = Risk factor is a highly probable contributor to the development of disease or outcome. Recommendation: Risk factor should be avoided or reduced, if possible. (Level A rating requires two or more consistent Class I studies all showing an effect size (R.R.) ≥ 2 with lower confidence limits >1. In addition, either (1) a causal inference is coherent with known biologic mechanisms and related scientific evidence or (2) findings clearly

demonstrate that higher doses of exposure increase likelihood of disease or outcome.)

Level B = Risk factor is a probable contributor to the development of disease or outcome. Recommendation: Risk factor avoidance or reduction (if possible) should be considered. (Level B rating requires at least one Class I study fulfilling other criteria above, OR two or more consistent Class II studies, showing an effect size (R.R. or O.R.) ≥ 1.5 with lower confidence limits >1 .)

Level C = Risk factor is a possible contributor to the development of disease or outcome. Recommendation: Risk factor avoidance or reduction (if possible) may be considered. (Level C rating requires 1 Class II or 2 or more Class III studies, showing effect estimate(s) with consistent significant departure(s) from null value.)

Level U = A causal relationship between the risk factor and disease or outcome is unproven or unsupported. Recommendation: None. (Evidence not meeting criteria for Class I – Class III.)

Classification of Evidence for Rating of a Prognostic Article:

Class I = A cohort study of a broad spectrum of persons at risk for developing the outcome (e.g., target disease, work status). The outcome is defined by an acceptable reference standard for case definition. The outcome is objective or measured by an observer who is masked to the presence of the risk factor. Study results allow calculation of measures of prognostic accuracy.

Class II = A case control study of a broad spectrum of persons with the condition compared to a broad spectrum of controls or a cohort study of a broad spectrum of persons at risk for the outcome (e.g., target disease, work status) where the data was collected retrospectively. The outcome is defined by an acceptable reference standard for case definition. The outcome is objective or measured by an observer who is masked to the presence of the risk factor. Study results allow calculation of measures of prognostic accuracy.

Class III = A case control study or a cohort study where either the persons with the condition or the controls are of a narrow spectrum where the data was collected retrospectively. The outcome is defined by an acceptable reference standard for case definition. The outcome is objective or measured by an observer who did not determine the presence of the risk factor. Study results allow calculation of measures of a prognostic accuracy.

Class IV = Studies not meeting Class I, II, or III criteria including consensus, expert opinion or a case report.

Classification of Evidence for Causality

The causality scheme is used to rate the risk of bias in studies when the clinical question requires a causal inference and a randomized controlled trial cannot be done for practical or ethical reasons. The classification emphasizes the need to establish an independent association between the risk factor and outcome after controlling for known confounding variables. Unlike a randomized controlled trial, studies rated by this scheme cannot control for unknown confounding variables.

Class I: Prospective cohort study design that satisfies these criteria: (a) groups studied are representative of population of interest ('broad spectrum'); (b) risk factors and outcomes are clearly defined with validated or generally accepted criteria, and measured independently or objectively; (c) comparison groups are matched for known possible confounding risk factors, or the effects of such confounders are controlled in the study analysis; and (d) measures of association are expressed (or can be calculated) as rate ratios, risk ratios, relative risks (R.R.) or population attributable risks with confidence intervals.

Class II: Retrospective cohort or case-control study designs that satisfy criteria (a), (b), and (c) above, in which (d) the measure of association may also be expressed (or can be calculated) as an odds ratio (O.R.) with confidence intervals.

Class III: Other cohort or case-control study designs in which groups studied represent a narrow spectrum of the population of interest, or the measure of association does not include an R.R. or O.R. but does include an aggregate measure such as a correlation or group mean with standard deviation or p-value. Criterion (b) above must still be satisfied. Obvious confounding is not evident.

Class IV: Studies not meeting criteria for Class I, II, or III. Specifically, studies that are non-comparative, unrepresentative of the population of interest, with major biases or confounding, lacking useful measures of effect, or lacking measures of effect estimate stability.

Notes: In addition to the criteria above, any causal inference requires that exposure to the risk factor precede the development of the outcome. In addition, there may be need to allow for an induction period. In translating evidence, a requirement of two or more studies implies that such studies should not include the same subjects. Exploratory studies involving multiple comparisons of a variety of exposures and outcomes may be rated lower if it is evident that the study was designed without an a priori hypothesis or focus upon the specific exposure and outcome of interest. Randomized clinical trials (RCTs) are equivalent to prospective cohort studies in which the risk of confounding has been minimized. Evidence from such studies may be considered Class I, provided it satisfies criteria (a), (b), and (d) above. Note, however, that it is preferable to apply the American Association of Neurology (AAN) criteria for therapeutic studies when classifying evidence pertaining to the experimental (treatment) variables of an RCT.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Epilepsy plus pregnancy

Guideline Category

Evaluation

Management

Risk Assessment

Treatment

Clinical Specialty

Family Practice

Neurology

Nursing

Obstetrics and Gynecology

Pharmacology

Intended Users

Advanced Practice Nurses

Health Care Providers

Health Plans

Managed Care Organizations

Patients

Pharmacists

Physician Assistants

Physicians

Guideline Objective(s)

To reassess the evidence for management issues related to the care of women with epilepsy (WWE) during pregnancy

To summarize evidence for three important issues regarding the clinical management of WWE who are pregnant or plan pregnancy:

What is the risk of major congenital malformations (MCMs) associated with intrauterine exposure to antiepileptic drugs in neonates

born to WWE?

What is the risk of adverse long-term cognitive outcomes in children born to WWE?

What is the risk of death, low birthweight, and low Apgar scores in neonates born to WWE?

Target Population

Women with epilepsy (WWE) who are pregnant or who are planning to become pregnant

Interventions and Practices Considered

1. Timing of antiepileptic drug (AED) exposure during pregnancy
2. Dose of AEDs during pregnancy
3. Effects on fetal development of AED monotherapy versus polytherapy in epilepsy during pregnancy
4. Effects on fetal development of particular AEDs in epilepsy during pregnancy
5. Effect of maternal epilepsy with and without fetal AED exposure on cognitive development of the offspring
6. Pregnancy risk assessment of fetal AED exposure in utero on cognitive function, small gestational growth, perinatal death, and depressed Apgar score

Major Outcomes Considered

Incidence of major congenital malformations (MCMs) in children of women with epilepsy (WWE)

Cognitive outcomes for children of WWE

Neonatal Apgar score

Fetal gestational growth rate

Perinatal mortality of children born to WWE

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

2009 Guideline

A literature search was performed using MEDLINE, MEDLINE-In-Process, Current Contents, Biologic Abstracts, and BIOSIS previews for relevant articles published between 1985 and December 2005. An updated search was performed from December 2005 through June 2007, with manual searches on some topics through February 2008. The arbitrary cutoff date of 1985 was chosen because these relatively recent articles were thought to reflect current practice and AED usage patterns and therefore be more applicable and reliable for this assessment than earlier reports. The search terms used were seizures/epilepsy, catamenial epilepsy, pregnancy, anticonvulsants, antiepileptic drugs, teratogenesis, birth defects, pregnancy registry, cognitive outcome, vitamin K, folate/folic acid, breastfeeding, oral contraceptives, polycystic ovary syndrome, hormone replacement therapy, menopause, perimenopause, and fertility. The search was confined to articles using human subjects and included all languages for which there was an abstract in English. A secondary search for missed references was done by reviewing the bibliographies of review articles and meta-analyses identified in the primary search.

The literature search yielded a total of 876 abstracts. To find relevant articles, two panel members screened each of the abstracts. If either panel member thought the article was potentially relevant, the full text was obtained for review. In general, abstracts were excluded from further analysis if they related to eclampsia rather than seizures due to epilepsy, related to basic mechanisms such as teratogenesis or placental AED metabolism,

or were unrelated to the questions posed by the panel.

From the abstracts, a total of 285 were selected for complete review. Four panel members reviewed the full text of the articles and identified those that were relevant to each clinical question. Seventy-eight relevant articles were identified by the literature search.

2013 Reaffirmation

The guideline developer searched Medline and Embase for studies published between 2009 and 2013 using the following search terms: women with epilepsy, pregnancy, seizure, teratogenesis, congenital malformations.

2016 Reaffirmation

The guideline developer searched Medline for studies published between January 2013 to April 2016 using the following search strategy: (((((((major congenital malformations) OR MCM) OR Cognition Disorders) OR Abnormalities, Drug-Induced) OR teratogenesis)))) AND Anticonvulsants) AND ((pregnancy) AND (((seizures) OR epilepsy) OR catamenial epilepsy)). Inclusion criteria were RCTs, humans only, relevant to clinical questions; exclusion criteria used to screen search results were the same as described in the 2009 published guideline.

Number of Source Documents

Questions related to major congenital malformations: 52 articles

Questions related to cognitive teratogenesis: 13 articles

Questions related to adverse perinatal outcomes: 13 articles

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Classification of Evidence for Rating of a Prognostic Article

Class I = A cohort study of a broad spectrum of persons at risk for developing the outcome (e.g., target disease, work status). The outcome is defined by an acceptable reference standard for case definition. The outcome is objective or measured by an observer who is masked to the presence of the risk factor. Study results allow calculation of measures of prognostic accuracy.

Class II = A case control study of a broad spectrum of persons with the condition compared to a broad spectrum of controls or a cohort study of a broad spectrum of persons at risk for the outcome (e.g., target disease, work status) where the data was collected retrospectively. The outcome is defined by an acceptable reference standard for case definition. The outcome is objective or measured by an observer who is masked to the presence of the risk factor. Study results allow calculation of measures of prognostic accuracy.

Class III = A case control study or a cohort study where either the persons with the condition or the controls are of a narrow spectrum where the data was collected retrospectively. The outcome is defined by an acceptable reference standard for case definition. The outcome is objective or measured by an observer who did not determine the presence of the risk factor. Study results allow calculation of measures of a prognostic accuracy.

Class IV = Studies not meeting Class I, II, or III criteria including consensus, expert opinion or a case report.

Classification of Evidence for Causality

The causality scheme is used to rate the risk of bias in studies when the clinical question requires a causal inference and a randomized controlled trial cannot be done for practical or ethical reasons. The classification emphasizes the need to establish an independent association between the risk factor and outcome after controlling for known confounding variables. Unlike a randomized controlled trial, studies rated by this scheme cannot control for unknown confounding variables.

Class I: Prospective cohort study design that satisfies these criteria: (a) groups studied are representative of population of interest ('broad spectrum'); (b) risk factors and outcomes are clearly defined with validated or generally accepted criteria, and measured independently or

objectively; (c) comparison groups are matched for known possible confounding risk factors, or the effects of such confounders are controlled in the study analysis; and (d) measures of association are expressed (or can be calculated) as rate ratios, risk ratios, relative risks (R.R.) or population attributable risks with confidence intervals.

Class II: Retrospective cohort or case-control study designs that satisfy criteria (a), (b), and (c) above, in which (d) the measure of association may also be expressed (or can be calculated) as an odds ratio (O.R.) with confidence intervals.

Class III: Other cohort or case-control study designs in which groups studied represent a narrow spectrum of the population of interest, or the measure of association does not include an R.R. or O.R. but does include an aggregate measure such as a correlation or group mean with standard deviation or p-value. Criterion (b) above must still be satisfied. Obvious confounding is not evident.

Class IV: Studies not meeting criteria for Class I, II, or III. Specifically, studies that are non-comparative, unrepresentative of the population of interest, with major biases or confounding, lacking useful measures of effect, or lacking measures of effect estimate stability.

Notes: In addition to the criteria above, any causal inference requires that exposure to the risk factor precede the development of the outcome. In addition, there may be need to allow for an induction period. In translating evidence, a requirement of two or more studies implies that such studies should not include the same subjects. Exploratory studies involving multiple comparisons of a variety of exposures and outcomes may be rated lower if it is evident that the study was designed without an a priori hypothesis or focus upon the specific exposure and outcome of interest. Randomized clinical trials (RCTs) are equivalent to prospective cohort studies in which the risk of confounding has been minimized. Evidence from such studies may be considered Class I, provided it satisfies criteria (a), (b), and (d) above. Note, however, that it is preferable to apply the American Association of Neurology (AAN) criteria for therapeutic studies when classifying evidence pertaining to the experimental (treatment) variables of an RCT.

Methods Used to Analyze the Evidence

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Panel Selection

A 20-member committee evaluated the available evidence based on a structured literature review and classification of relevant articles published between January 1985 and June 2007.

Study Classification and Measures of Effect

Articles were classified according to the American Academy of Neurology (AAN) classification of evidence schemes for prognostic articles and articles of causality (see the "Rating Scheme for the Strength of the Evidence" field). Articles were classified separately by four panel members. Disagreements on categorization of the articles were resolved by discussion and consensus.

Analysis of Evidence

To attain a Class I or II rating, the study must have accounted for confounding by maternal age and socioeconomic status.

The question regarding risk of major congenital malformations (MCMs) due to antiepileptic drugs (AEDs) taken during the first trimester was addressed by including only studies where WVE not taking AEDs served as comparators.

For the subsequent questions, the evaluation focused on the risks of AEDs compared to each other, or findings specific to an individual AED such as a dose-malformation relationship. Therefore, three studies used in answering these questions include the offspring of mothers who took AEDs for various indications.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

2009 Guideline

The American Academy of Neurology (AAN) assembled a panel of experts including epileptologists, general neurologists, and doctors in

pharmacy with expertise in antiepileptic drugs. Panel members with expertise in obstetrics, obstetrical nursing, and teratology were also included.

The Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and American Epilepsy Society developed a set of clinical questions relevant to the evaluation of management issues related to the care of women with epilepsy (WWE) during pregnancy.

The strength of the practice recommendations was directly linked to the class of evidence using the scheme described in the "Rating Scheme for the Strength of the Recommendations" field.

2013 Reaffirmation

The AAN assesses their clinical practice guidelines every 2 years to determine whether new literature has been published that would warrant an update. The following steps are taken:

- Biennial correspondence is sent to all authors and the facilitator.
- An updated literature search and a review of methodological soundness are performed by a Guideline Development Subcommittee (GDS) member. (Note: The search should specifically seek to identify new evidence that would change the conclusions in the systematic review or recommendations in the CPG.)

All documents biennially reviewed by the GDS that don't require an update are reaffirmed. See the AAN [Clinical Practice Guideline Process Manual](#) for additional information.

2016 Reaffirmation

A Guideline Development, Dissemination, and Implementation (GDDI) Subcommittee member who had expertise in epilepsy conducted a targeted literature search for high quality studies using the same criteria as presented in the original guideline. The GDDI reviewer and the subcommittee reviewed the new evidence and determined that the following three criteria were met: 1. There is no new evidence that would alter conclusions or recommendations in the guideline since the last literature search, 2. Guideline methodology is sound and current methodology is not substantially different, and 3. No significant practice variation relevant to the guideline currently exists.

Rating Scheme for the Strength of the Recommendations

Classification of Recommendations

The strength of practice recommendations is linked directly to the level of evidence:

Level A = Established as effective, ineffective, or harmful (or established as useful/predictive or not useful/predictive) for the given condition in the specified population. (Level A rating requires at least two consistent Class I studies.*)

Level B = Probably effective, ineffective, or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specified population. (Level B rating requires at least one Class I study or two consistent Class II studies.)

Level C = Possibly effective, ineffective, or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population. (Level C rating requires at least one Class II study or two consistent Class III studies.)

Level U = Data inadequate or conflicting; given current knowledge, treatment (test, predictor) is unproven.

*In exceptional cases, one convincing Class I study may suffice for an "A" recommendation if: 1) all criteria are met, 2) the magnitude of effect is large (relative rate improved outcome >5 and the lower limit of the confidence interval is >2).

Classification of Recommendations for Causality

Level A = Risk factor is a highly probable contributor to the development of disease or outcome. Recommendation: Risk factor should be avoided or reduced, if possible. (Level A rating requires two or more consistent Class I studies all showing an effect size (R.R.) ≥ 2 with lower confidence limits >1 . In addition, either (1) a causal inference is coherent with known biologic mechanisms and related scientific evidence or (2) findings clearly demonstrate that higher doses of exposure increase likelihood of disease or outcome.)

Level B = Risk factor is a probable contributor to the development of disease or outcome. Recommendation: Risk factor avoidance or reduction (if possible) should be considered. (Level B rating requires at least one Class I study fulfilling other criteria above, OR two or more consistent Class II studies, showing an effect size (R.R. or O.R.) ≥ 1.5 with lower confidence limits >1 .)

Level C = Risk factor is a possible contributor to the development of disease or outcome. Recommendation: Risk factor avoidance or reduction (if possible) may be considered. (Level C rating requires 1 Class II or 2 or more Class III studies, showing effect estimate(s) with consistent significant departure(s) from null value.)

Level U = A causal relationship between the risk factor and disease or outcome is unproven or unsupported. Recommendation: None. (Evidence not meeting criteria for Class I – Class III.)

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

The Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and American Epilepsy Society reviewed and approved a draft of the article. The draft was next sent to members of the Practice Committee of the American Academy of Neurology and American Epilepsy Society for further review and then to Neurology® for peer review. Boards of the American Academy of Neurology and American Epilepsy Society reviewed and approved the final version of the article. At each step of the review process, external reviewers' suggestions were explicitly considered. When appropriate, the expert panel made changes to the document.

This guideline was approved by the Quality Standards Subcommittee April 15, 2008; by the Therapeutics and Technology Assessment Subcommittee December 17, 2007; by the Practice Committee January 25, 2009; and by the AAN Board of Directors March 25, 2009.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Minimizing antiepileptic drug exposure during pregnancy may reduce the teratogenic and adverse perinatal risks of these drugs.

Potential Harms

If the change from valproate to another antiepileptic drug (AED) is planned, it seems prudent to do this well before pregnancy to make sure the new treatment adequately prevents seizures. Changing to another antiepileptic drug during pregnancy poses risk of allergy, other serious adverse reactions, and polytherapy exposure. Once a patient is pregnant, changing from valproate several weeks into gestation will not avoid the risk of major congenital malformations, since this phenomenon occurs very early in pregnancy. This may also apply to cognitive teratogenesis, since the timing of exposure related to this adverse outcome is unknown.

Although the risks of seizures during pregnancy have not been systematically studied, discontinuing AEDs may expose the mother and fetus to physical injury from accidents arising from partial or generalized seizures.

Qualifying Statements

Qualifying Statements

This statement is provided as an educational service of the American Academy of Neurology (AAN). It is based on an assessment of current scientific and clinical information. It is not intended to include all possible proper methods of care for a particular neurologic problem or all legitimate criteria for choosing to use a specific procedure. Neither is it intended to exclude any reasonable alternative methodologies. The AAN recognizes that specific patient care decisions are the prerogative of the patient and the physician caring for the patient, based on all of the circumstances involved. The clinical context section is made available in order to place the evidence-based guideline(s) into perspective with current practice habits and challenges. No formal practice recommendations should be inferred. The findings and conclusions in the report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Foreign Language Translations

Patient Resources

Quick Reference Guides/Physician Guides

Resources

Slide Presentation

Staff Training/Competency Material

Wall Poster

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Living with Illness

Staying Healthy

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

Harden CL, Meador KJ, Pennell PB, Hauser WA, Gronseth GS, French JA, Wiebe S, Thurman D, Koppel BS, Kaplan PW, Robinson JN, Hopp J, Ting TY, Gidal B, Hovinga CA, Wilner AN, Vazquez B, Holmes L, Krumholz A, Finnell R, Hirtz D, Le Guen C. Practice parameter update: management issues for women with epilepsy--focus on pregnancy (an evidence-based review): teratogenesis and perinatal outcomes. Report of the Quality Standards Subcommittee [trunc]. *Neurology*. 2009 Jul 14;73(2):133-41. [45 references] [PubMed](#)

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

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Guideline Developer(s)

American Academy of Neurology - Medical Specialty Society

American Epilepsy Society - Disease Specific Society

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American Academy of Neurology (AAN)

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Guideline Committee

The Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee

Composition of Group That Authored the Guideline

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Financial Disclosures/Conflicts of Interest

The American Academy of Neurology (AAN) is committed to producing independent, critical and truthful clinical practice guidelines (CPGs). Significant efforts are made to minimize the potential for conflicts of interest to influence the recommendation of this CPG. To the extent possible, the AAN keeps separate those who have a financial stake in the success or failure of the products appraised in the CPGs and the developers of the guidelines. Conflict of interest forms were obtained from all authors and reviewed by an oversight committee prior to project initiation. AAN limits the participation of authors with substantial conflicts of interest. The AAN forbids commercial participation in, or funding of, guideline

projects. Drafts of the guidelines have been reviewed by at least three AAN committees, a network of neurologists, Neurology peer reviewers, and representatives from related fields. The AAN Guideline Author Conflict of Interest Policy can be viewed at www.aan.com

Disclosure

The authors report the following conflicts of interest: Dr. Harden has served on the scientific advisory board of Cyberonics, GlaxoSmithKline, UCB Pharma, Valeant, and SK Pharmaceuticals and on the speakers' bureau of GlaxoSmithKline, Pfizer, UCB Pharma, and Abbott. She serves as an editor of *Epilepsy Currents* and receives publishing royalties from Elsevier. Dr. Harden has received research funding from Forest, UCB Pharma, Ortho McNeil, and NIH/NINDS. Dr. Harden sees women with epilepsy in her office practice. Dr. Meador serves as a journal editor for *Neurology*, *Journal of Clinical Neurophysiology*, *Cognitive and Behavioral Neurology*, *Epilepsy & Behavior*, *Epilepsy Currents*, and *Epilepsy.com*. He has received research funding from NIH/NINDS, GlaxoSmithKline, Eisai, Marius, Myriad, Neuropace, SAM Technology, and UCB Pharma. Dr. Meador estimates that 30-40% of his clinical effort is spent on EEGs and the clinical care of patients with epilepsy. Dr. Pennell has served on the Expert Panel for the Keppra Pregnancy Registry sponsored by UCB Pharma. She has received funding for travel from the Northeast Regional Epilepsy Group for speaking at their 2008 Epilepsy Symposium, by the UK Research Council for speaking at the Epilepsy Research UK International Expert Workshop, by UCB Pharma for attending the Executive Panel meeting for the Pregnancy Registry, by the American Epilepsy Society for attending the Board of Directors' Meeting, by the Epilepsy Foundation for attending the Board of Directors' and orientation meetings, by the Long Island Jewish Hospital for lecturing at Neurology Grand Rounds, by Duke University for lecturing at Neurology Grand Rounds, by Brigham and Women's Hospital for lecturing at the Epilepsy Research Conference, by the Milken foundation for attending Pregnancy Registry meetings, and by Massachusetts General Hospital for speaking at the Annual Teratogens Course. She has received honoraria from Journal Watch Neurology for a contributing article, paid for by Massachusetts Medical Society, *NEJM*, for review for the *Lancet Neurology*, the Northeast Regional Epilepsy group for speaking at 2008 Epilepsy Symposium, North Shore Long Island Jewish Health system, Duke University, University of Maryland, the Massachusetts General Hospital for speaking at the postgraduate course in Human Teratogens, and the AAN for speaking and directing annual courses. Dr. Pennell has served as a contributing editor for *Epilepsy Currents* and is on the editorial board of *Epilepsia*. Dr. Pennell has received research support from UCB Pharma, Marinus Pharmaceuticals, NIH, NINDS, NIMH, CDC, and Emory University Research Council. Dr. Hauser has served on the scientific advisory board of Ovation and Valeant. He has served on the editorial board of *Acta Neurologica Scandinavica*, *Neuroepidemiology*, and *Epilepsy Research*. 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Dr. French is the president of the Epilepsy Study Consortium, which receives money from multiple pharmaceutical companies (including GlaxoSmithKline, UCB Pharma, Johnson and Johnson, Cyberonics, Schwarz Pharma, Ortho McNeil, Eisai, Jazz Pharmaceuticals, Ovation Pharmaceuticals, Endo Pharmaceuticals, Bial Pharmaceuticals, Neurovista, Valeant Pharmaceuticals, Icagen, Supernus, Intranasal, SK Pharmaceuticals, Taro Pharmaceuticals, Neurotherapeutics, Sepracor, and Novartis) and she consults on behalf of the consortium. Dr. French has received research funding from Johnson and Johnson, Eisai, UCB Pharma, SK Pharmaceuticals, Valeant, Pfizer, NIH, and Epilepsy Research Foundation. Dr. Wiebe serves on the editorial board of *Neurology*, *Epilepsia*, *Epilepsy & Behavior*, and *Canadian Journal of Neurological Sciences*. Dr. Thurman is an employee of the CDC. Dr. Koppel reports no disclosures. Dr. Kaplan has served on the speakers' bureau of UCB Pharma, GSK, and Ortho McNeil. He serves as an associate editor for *Neurophysiologie Clinique*, *Journal of Clinical Neurophysiology*, and *Epilepsia*. He receives royalties from Demos Publications for the books *Neurological Disease in Women*, *Epilepsy A to Z*, *Imitators of Epilepsy*, and *Nonconvulsive Status Epilepticus*. He has received speaker honoraria from Medical College of South Carolina, Duke University, and Medical College of Virginia, has received research funding from NIH, Schwarz, Ortho McNeil, and Pfizer, and has acted as a consultant for Schering-Plough and Infinite Biological Technologies. Dr. Robinson reports no disclosures. Dr. Hopp receives royalties from UpToDate.com electronic medical journal. She has been on the speakers' bureau of UCB Pharma and GlaxoSmithKline. Dr. Hopp has given testimony in a medico-legal case. Dr. Ting served on the scientific advisory board of UCB Pharma and has received honoraria from the Epilepsy Foundation of America. Dr. Gidal has served on the scientific advisory board for GlaxoSmithKline, UCB Pharma, and Abbott Labs and served as an editor for *Epilepsy & Behavior*, *The Annals of Pharmacotherapy*, and *Pharmacist's Letter*. Dr. Gidal has received research support from UCB Pharma. Dr. Hovinga estimates less than 10% of his clinical effort is spent on pharmacology consults. Dr. Wilner has served on the scientific advisory board of and received funding for travel from GlaxoSmithKline. He receives royalties from Demos Publications for *Epilepsy: 199 Answers* and *Epilepsy in Clinical Practice*. He receives board of directors compensation from GlaxoSmithKline. Dr. Vazquez has served on the scientific advisory board of Eisai, UCB, GSK, and Ortho McNeil. She has received honoraria from UCB, GSK, Ortho McNeil, and Eisai. Dr. Vazquez has served on a speakers' bureau for Eisai, GSK, Ortho McNeil, UCB, and Novartis. Dr. Holmes receives research support from Abbott Labs, Eisai, Novartis, Ortho McNeil, and Pfizer. Dr. Krumholz has served on the Department of Transportation Expert Panel on Commercial Drivers and

Epilepsy and has served on the editorial board of *The Neurologist* and *Clinical EEG and Neuroscience*. He has received honoraria from the Robert Wood Johnson Medical School for grand rounds. Dr. Finnell has served on the scientific advisory board of the NEAD study at Emory University, the University of Houston Center for Life Sciences Technology, the NIH, and the NIEHS National Advisory Environmental Health Sciences Council. He has received funding for travel from Fundacion BBVA, NIEHS National Advisory Environmental Health Sciences Council, IKMC Steering Committee, European Epilepsy Meeting, NIH, and AES. Dr. Finnell has served as a journal editor for *Birth Defects Research Part A* and holds a patent on folate receptor autoantibody assay. He has received honoraria from McGill University-Montreal Neurological Institute and has received research funding from the Centers for Disease Control and Prevention for the National Birth Defects Prevention Study and the Methodist Hospital Research Institute. Dr. Finnell has given expert testimony, prepared affidavits, and acted as a witness regarding legal proceedings related to the topic of this manuscript. Dr. Hirtz reports no disclosures. Ms. Le Guen reports no disclosures.

Guideline Endorser(s)

Child Neurology Society - Medical Specialty Society

Guideline Status

This is the current release of the guideline.

The American Academy of Neurology reaffirmed the currency of this guideline in 2016.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Electronic copies: A list of American Academy of Neurology (AAN) guidelines, along with a link to a Portable Document Format (PDF) file for this guideline, is available at the [AAN Web site](#) .

Print copies: Available from the AAN Member Services Center, (800) 879-1960, or from AAN, 201 Chicago Avenue South, Minneapolis, MN 55415.

Availability of Companion Documents

The following are available:

- Management issues for women with epilepsy—focus on pregnancy (an evidence-based review): teratogenesis and perinatal outcomes. AAN summary of evidence-based guideline for clinicians. St. Paul (MN): American Academy of Neurology (AAN). 2009. 2 p. Available from the [AAN Web site](#) .
- Practice parameter update: management issues for women with epilepsy—focus on pregnancy (an evidence-based review): teratogenesis and perinatal outcomes. Case study. St. Paul (MN): American Academy of Neurology. 2009. 6 p. Available from the [AAN Web site](#) .
- Practice parameter update: management issues for women with epilepsy—focus on pregnancy (an evidence-based review): teratogenesis and perinatal outcomes. Wall poster. St. Paul (MN): American Academy of Neurology. 2009. 2 p. Available from the [AAN Web site](#) .
- Practice parameter update: management issues for women with epilepsy—focus on pregnancy (an evidence-based review). Slide presentation. St. Paul (MN): American Academy of Neurology. 2009. 105 p. Available from the [AAN Web site](#) .
- Practice parameter update: management issues for women with epilepsy—focus on pregnancy (an evidence-based review): teratogenesis and perinatal outcomes. Korean translation. St. Paul (MN): American Academy of Neurology. 2009. 10 p. Available from the [AAN Web site](#) .
- AAN guideline development process [online]. St. Paul (MN): American Academy of Neurology. Available from the [AAN Web site](#) .

Patient Resources

The following are available:

- Women with epilepsy: drug risks and safety during pregnancy. AAN summary of evidence-based guideline for patients and their families. St. Paul (MN): American Academy of Neurology (AAN). 2009. 2 p. Electronic copies: Available in [English](#) and [Spanish](#) in Portable Document Format (PDF) from the AAN Web site.
- Women with epilepsy: drug risks to the fetus or baby during pregnancy. AAN summary of evidence-based guideline for patients and their families. St. Paul (MN): American Academy of Neurology (AAN). 2009. 1 p. Electronic copies: Available in [English](#) and [Spanish](#) in Portable Document Format (PDF) from the AAN Web site.

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC Status

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